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Clinical paper

The effect of intravenous adrenaline on electrocardiographic changes during resuscitation in patients with initial pulseless electrical activity in out of hospital cardiac arrest

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Abstract

Introduction: Presence of electrocardiographic rhythm in the absence of palpable pulses defines pulseless electrical activity (PEA) and the electrocardiogram (ECG) may provide a source of information during resuscitation. The aim of this study was to examine the development of ECG characteristics during advanced life support (ALS) from Out-of-hospital cardiac arrest (OHCA) with initial PEA, and to explore the potential effects of adrenaline on these characteristics.

Methods: Patients with OHCA and initial PEA, part of randomized controlled trial of ALS with or without intravenous access and medications, were included. A total of 4840 combined observations of QRS complex rate (heart rate) and width were made by examining defibrillator recordings from 170 episodes of cardiac arrest.

Results: We found Increased heart rate (47 beats per minute) and reduced QRS complex width (62 ms) during ALS in patients who obtained return of spontaneous circulation (ROSC); while patients who received adrenaline but died increased their heart rate (22 beats per minute) without any concomitant decrease in QRS complex width.

Conclusion: ECG changes during ALS in cardiac arrest were associated with prognosis, and the administration of adrenaline impacted on these changes.

Keywords: Pulseless electrical activity, PEA, Electrocardiographic, ECG, Adrenaline, Epinephrine, Cardiac arrest, Advanced life support

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Introduction

Pulseless electrical activity (PEA), defined as an organized electrocardiographic rhythm in the absence of palpable pulses, is the presenting rhythm in about one quarter of patients with out of hospital cardiac arrest (OHCA).[1–4] The electrocardiogram (ECG) reflects the electric function of the myocardium.[5] Changes in the ECG may represent a source of information during the provision of advanced life support (ALS) to such patients.

In an observational study of in-hospital cardiac arrest (IHCA), we found an increase in PEA heart rate and a gradual narrowing of the QRS width the last 6–12 minutes (min) before return of spontaneous circulation (ROSC).[6] These findings may have prognostic importance, as well as raising questions about the electromechanical properties of the heart during PEA.

Administration of adrenaline (epinephrine) has been shown to increase the proportion of patients who achieve ROSC without increasing long term survival.[4,7,8] In one recent randomized controlled trial of adrenaline versus placebo in OHCA a larger proportion with ROSC was found in the adrenaline group, but long term survival was also higher in the adrenaline group.[9] Some authors have argued that adrenaline to patients with non-shockable rhythms (asystole and PEA) is as essential as defibrillation to shockable rhythms (ventricular fibrillation —VF and pulseless ventricular tachycardia —VT).[10,11] In cardiac arrest the presumed main effect of adrenaline is to improve coronary perfusion pressure by increasing aortic diastolic pressure.[12] A general effect of adrenaline is an increase in heart rate.[13] Despite being a routine drug in cardiac arrest, the immediate effect of adrenaline on ECG characteristics during ALS has not been studied. We hypothesized that possible beneficial effects of adrenaline could be associated with change in heart rate. The aim of this study was to investigate the development of ECG characteristics during ALS in patients with OHCA and initial PEA, and the effect of adrenaline on these characteristics.

Material and methods

Data collection and handling

A randomized controlled trial was conducted at the Oslo Emergency Medicine Services between 2003 and 2008 in adult OHCA patients. Patients were randomized to ALS with and without intravenous access and drug administration. Main outcomes were ROSC and survival to hospital discharge.[4,14] Patients from this study with initial PEA were included in the current sub-group analysis. Electronic signal data from Lifepak 12 defibrillators (LP 12, Physio Control, Medtronic, Redmond, WA, USA), clinical data from Utstein style cardiac arrest forms and data from hospital records acquired for the original study were analysed.[4]

Electrocardiographic characteristics

ECG and transthoracic impedance (TTI) data from LP 12 were analysed using Matlab (R2017b, Math Works Inc., Natick, MA), and annotated in terms of clinical states (Asystole, PEA, VF/VT, ROSC) as described in a previous publication.[15]

The ECG and TTI signals were plotted against time, QRS-rates (heart rate) and -widths were measured during pauses in chest compressions for any reason (including at end of efforts or when sustained ROSC was obtained), as long as measurable QRS complexes existed. The QRS width was defined as the interval between the initial deflection from the baseline towards the Q- or R-wave and the beginning of the ST-interval on the ECG. In cases when no obvious transition from the QRS to the ST-interval could be seen, the point where the ECG tracing crossed the baseline towards the T-wave was considered the QRS end-point, as described previously.[6] Each QRS width measurement was coupled to an instantaneous heart rate, calculated from the distance between the QRS complex in question and the succeeding QRS complex.

Statistical analysis

Patients were grouped by ROSC status, the ROSC group comprising all patients with ROSC at hospital admission; and by whether intravenous adrenaline was actually given. We disregarded the intention-to-treat status in the original study, as the biological effect of adrenaline was of main interest in this subgroup analysis.

We expected that heart rate and QRS width would be correlated; this was tested using Pearson's product moment correlation.

First, we investigated the combined change in heart rate and QRS width using bivariate analysis of variance (MANOVA)[16] according to ROSC and adrenaline. Here we employed the first and last 15 s averaged heart rate and QRS width in each patient. To satisfy the requirement of bivariate normality and homoscedasticity, we applied a square root transformation after adding a constant term to avoid negative values. Q–Q plots were satisfactory.

Second, we modelled the 15-s final averaged heart rate and QRS width separately using a linear model[17] using the initial 15-s heart rate or QRS width as continuous covariates, and ROSC and adrenaline as factors.

Third, to visualize the average development of the ECG characteristics for the last 12 min preceding ROSC or termination of ALS efforts, we fitted additive mixed effects models[18] of heart rate and QRS width in each group; with time as the fixed effect covariate, and patient identity as random effect. We specified autocorrelated residuals (which improved model fit) as we expected that measurements closer to each other in time would be more similar than measures further apart. The additive mixed models fit penalized regression splines to the data, by a process of cross validation.[18]

All measurements of heart rate and QRS that were made at or later than 12 min before ROSC or end of ALS were included in this model, irrespective of timing. No attempts were made to balance data with respect to number of or timing of measurements between patients.

The software R version 3.4.3,[19] running in RStudio version 1.1.419, with the packages *mcgv, nlme* and *ellipse*, and the software Stata,[20] were utilized for the statistical analyses. A p-value less than 0.05 was considered to indicate statistical significance.

Ethics

The Regional Committees for Medical and Health Research Ethics approved the study. The original study was registered at clinical-trials.gov with identifier NCT00121524.

Results

Two-hundred and thirty-three patients had initial PEA in the original study, of whom 170 patients (73%) were included in the current analysis. Patients were excluded due to missing defibrillator file (n = 59) or that defibrillator files were illegible (n = 4). ROSC at admission to hospital was present in 41 patients (24%) and adrenaline

was administered to 101 (59%) of the included patients. A total of 4840 combined observations of QRS rate and width were made from the defibrillator files from the included patients. Demographic and clinical data are presented in Table 1. The groups varied in size: the 'no ROSC' groups were larger. Otherwise, there was a notable difference in duration of ALS between the 'no adrenaline ROSC' group and all other groups, with shorter duration of ALS in this group. The 'no adrenaline ROSC' group also consisted of all but one male.

Changes in heart rate and QRS complex width from start to end of ALS

Heart rate and QRS width were found to be negatively correlated (Pearson's r: −0.35, $p < 0.0001$). Bivariate analysis of the combined change of heart rate and QRS width from the beginning to the end of ALS showed that these variables were significantly associated with both whether ROSC was obtained and whether adrenaline was administered ($p < 0.001$ for both). There was no evidence of interaction between ROSC and adrenaline status ($p = 0.86$). Univariate analysis of mean final heart rate or QRS width separately showed that the final mean heart rate was dependent on the mean initial heart rate (coefficient 0.28, $p = 0.01$), ROSC (46.6 bpm increase with ROSC, $p < 0.0001$), and adrenaline (21.7 bpm increase with adrenaline, $p < 0.0001$). Final mean QRS width depended on mean initial QRS width (coefficient 0.45, $p < 0.0001$) and ROSC (62 ms less with ROSC, $p < 0.0001$), but not adrenaline ($p = 0.4$). There was no evidence of interaction between ROSC and adrenaline status in the univariate analyses ($p = 0.8$ and 0.72 for heart rate and QRS width respectively).

The observed mean changes in heart rates and QRS widths are illustrated as arrows in Fig. 1. The individual measurements of QRS widths and heart rates at the beginning, during, and at the end of ALS are presented as bivariate scatterplots in Fig. 1; there was considerable variation in these measurements.

Time course of heart rate and QRS complex width during the last 12 min of ALS

The expected heart rate and QRS width during the last 12 min of ALS before ROSC or end of ALS efforts are presented in Fig. 2, based on predictions from the additive mixed models. In both the 'adrenaline' and the 'no adrenaline ROSC' groups, a marked rise in heart rate occurred between 3–6 min before ROSC. Heart rate increased slightly in a linear fashion in the 'adrenaline no ROSC' group, but was unchanged towards the end of ALS efforts in the 'no adrenaline no ROSC' group. We observed a sharp decrease in QRS width the last 6 min in the 'adrenaline ROSC' group. In the 'no adrenaline ROSC' group a more gradual narrowing of QRS widths occurred during the last 12 min of ALS. In both no-ROSC groups QRS width increased slightly.

Discussion

To our knowledge, this is the first study to examine changes in ECG characteristics during ALS in patients with OHCA and initial PEA for the duration of ALS. It is a secondary analysis of a randomized controlled trial of intravenous access versus no intravenous access in

Table 1 – Demographic and clinical data, stratified on ROSC and adrenaline status. (n = number, yrs: years, min: minute, IQ range: Interquartile range, mg: milligram).

	Return of spontaneous circulation (n = 41)		No return of spontaneous circulation (n = 129)	
	Adrenaline (n = 29)	No adrenaline (n = 12)	Adrenaline (n = 72)	No adrenaline (n = 57)
Age (yrs), median (IQ range)	61 (56–75)	65 (62–75)	78 (56–83)	77 (65–85)
Males, n (%)	15 (52)	11 (92)	47 (36)	34 (60)
Location				
Home, n (%)	20 (69)	5 (42)	41 (57)	41 (72)
Public, n (%)	5 (17)	5 (42)	20 (28)	11 (21)
Work, n (%)	0 (0)	1 (8)	1 (1)	0 (0)
Other, n (%)	4 (14)	1 (8)	10 (14)	5 (9)
Witnessed by layperson, n (%)	19 (66)	8 (67)	31 (43)	38 (67)
Witnessed by paramedic, n (%)	6 (21)	1 (8)	28 (38)	6 (11)
Bystander CPR, n (%)	12 (41)	3 (25)	26 (36)	27 (47)
Response time (min), median (IQ range)	7.9 (5.3–9.0)	10.6 (6.3–11.4)	6.1 (0–8.7)	9.6 (6.6–11.3)
Duration of ALS (min), median (IQ range)	20 (12.5–28.1)	6.7 (5.2–11.5)	26.5 (19.1–31.9)	21.4 (14.4–28.9)
Compression rate (/min), median (IQ range)	117 (112–120)	115 (112–126)	119 (112–126)	112 (107–120)
Hands off ratio, median (IQ range)	0.15 (0.1–0.26)	0.18 (0.12–0.28)	0.17 (0.12–0.25)	0.20 (0.13–0.29)
Defibrillation at least once, n (%)	4 (14)	0 (0)	24 (33)	7 (12)
Intubated, n (%)	27 (93)	9 (75)	62 (86)	45 (79)
Intravenous access, n (%)	29 (100)	8 (67)	71 (99)	7 (12)
Adrenaline dose (mg), median (IQ range)	2 (1–3)	0 (0)	3 (2–5)	0 (0)
Atropine, n (%)	8 (28)	0 (0)	35 (49)	2 (4)
Amiodarone, n (%)	0 (0)	1 (8)	9 (13)	0 (0)
Admitted to hospital, n (%)	29 (100)	12 (100)	22 (30)	11 (19)
Discharged from hospital alive, n (%)	1 (3)	3 (25)	0 (0)	1 (2)[a]

Missing data: witnessed (n = 1), age (n = 1), adrenaline dose (n = 19), duration of ALS (n = 1), IV access (n = 1).
[a] One patient without pre-hospital ROSC but admitted to hospital under ALS survived to hospital discharge.

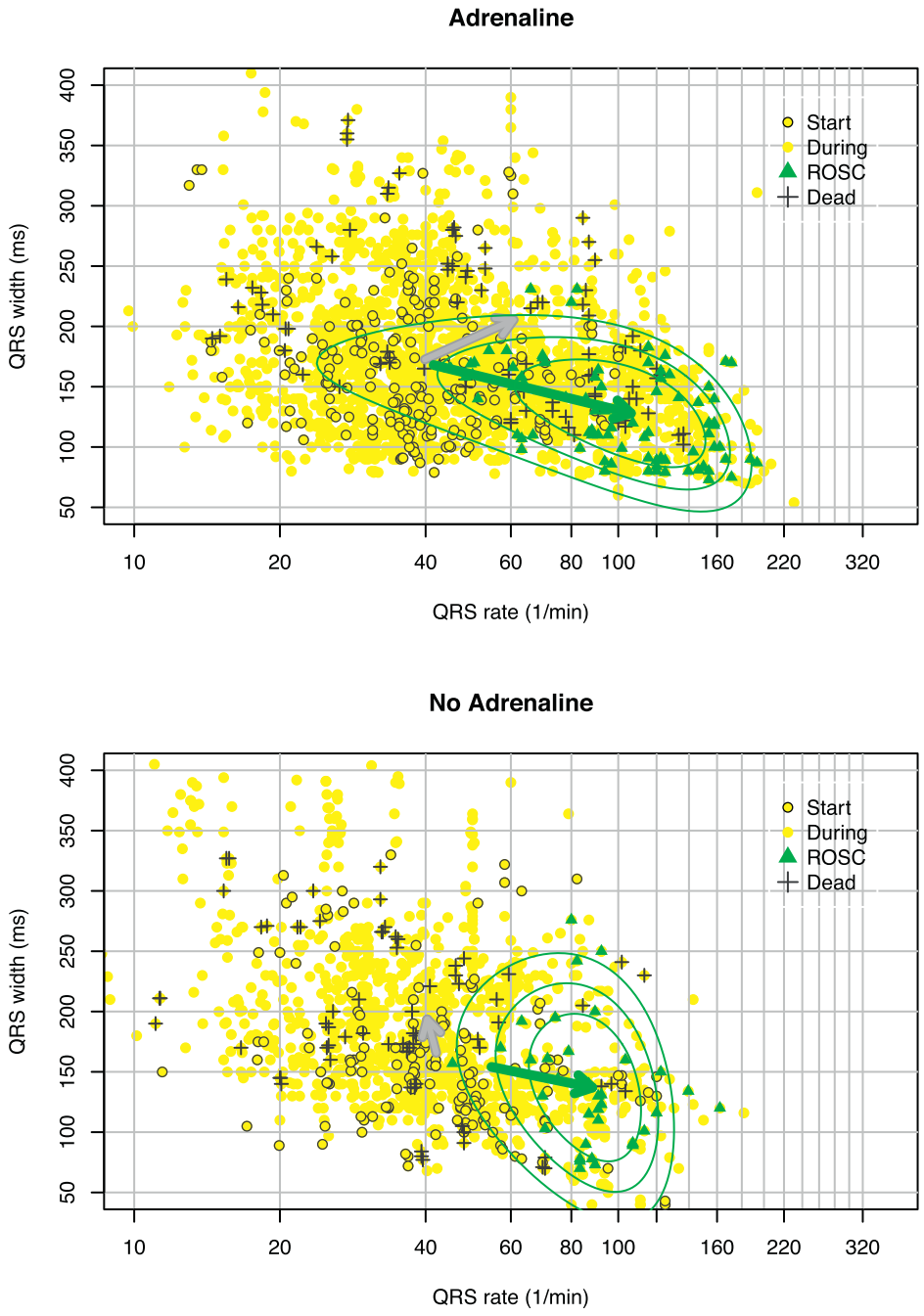

Fig. 1 – Bivariate Plot of Heart rate and QRS width, ms: milliseconds, min: minutes. The heart rate axis was log transformed for visualization purposes.
Top figure: adrenaline group, lower figure no-adrenaline group.
The circles, dots and plus signs represent individual measurements of heart rate and QRS width at the beginning, during and at the end of ALS. These are not grouped by either patient or ROSC status, but illustrate the variability in the individual measurements.
The arrows represent mean change from start of ALS (base of arrow) to end of ALS (tip of arrow). Green arrows represent the ROSC groups, grey arrows represent the no ROSC groups.
The green ellipses represent the 50, 75 and 90% coverage areas for the ROSC-groups' end points.

ALS, where adrenaline was only administered to the intravenous access group.

We discovered that patients who obtained ROSC had increased heart rates and decreased QRS widths before ROSC, in contrast to patients who were declared dead on scene. Patients given adrenaline had a larger mean change in heart rate, but a similar change in QRS width compared to patients who did not get adrenaline, both in the ROSC and no ROSC groups.

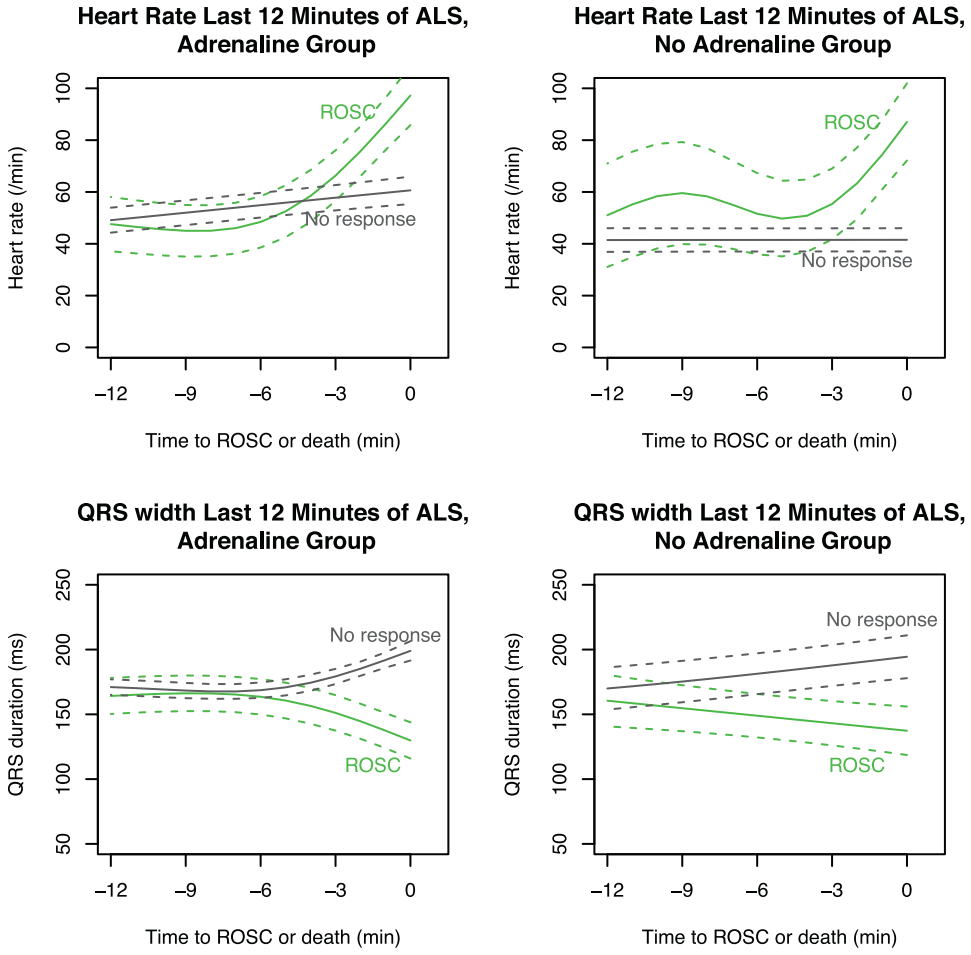

Fig. 2 – Development of heart rate (top) and QRS width (bottom) for the last 12 min of ALS, i.e. the last 12 min before sustained ROSC (green), or before ALS efforts were stopped (grey/ No response), according to the additive mixed effects model. The adrenaline group is at the left, the no-Adrenaline group is at the right. Dashed lines: 95% confidence intervals. (ms: milliseconds. min: minutes. ROSC: return of spontaneous circulation").

Overall, the pattern of increase in heart rate and narrowing of QRS width in the ROSC groups are consistent with the findings of our earlier study of in-hospital cardiac arrest with initial PEA.[6]

The increase in heart rate in the ROSC groups occurred mainly during the last 3–6 min before ROSC was obtained. In patients who received adrenaline, the QRS narrowed simultaneously with the increase in heart rate, while QRS width decreased more gradually in the 'no adrenaline ROSC' group. Interestingly, in patients who did not obtain ROSC; those who received adrenaline differed markedly from those who did not, in that heart rate increased in the adrenaline group while remaining unchanged in the no-adrenaline group.

The change of heart rate and QRS width in the ROSC groups in this study were changes towards more normal values. This is in line with other studies of OHCA that essentially have found a higher prevalence of normal initial ECG characteristics in survivors presenting with PEA.[21–23]

The mainly broad complexes without detectable atrial activity seen in this study were most likely of ventricular origin. Subendocardial Purkinje cells have been implicated in arrhythmogenesis after myocardial infarction, and has been observed to function as pacemakers in the damaged heart in dogs.[24] It has been shown that in ventricular Purkinje cells that survive acute ischemia, the resting membrane potential is less negative, with increased automaticity and prolonged action potentials.[25] Further, adrenaline has been shown to increase action potential generation in these cells, an effect that was abolished using a beta-blocking drug.[26]

Though heart rate and QRS width were inversely correlated in this study, the development over time differed. Both these variables depend on the electrical function of the heart, and are somewhat correlated in healthy humans as well, though the exact mechanisms are unclear.[27] Based on our results we speculate that the QRS width more closely reflects the underlying physiological state of the myocardium, but that the heart may be able to respond with increased heart rate to adrenaline even if the underlying metabolic state of the myocardium is not improved. This could theoretically explain the increase in heart rate and QRS width seen in the 'adrenaline no ROSC' group. The different pattern of QRS width narrowing in the ROSC groups may be due to a more sudden improvement in myocardial state in the 'adrenaline ROSC' group, perhaps, again theoretically, by a rapid adrenaline mediated increase in coronary perfusion pressure.

Based on the occurrence of ROSC in the adrenaline and no adrenaline groups, a larger number of survivors to hospital discharge in the adrenaline group would be expected. However, an increased proportion of patients with ROSC but a lesser or no

increase in the proportion of survivors in the long term has repeatedly been shown in both observational studies and randomized clinical trials of adrenaline in ALS with undifferentiated initial rhythms.[7–9] This was also the main result of the study for which the data analysed in the current study was gathered.[4] A number of factors may contribute to this, one of which is a possible detrimental effect of adrenaline on long term myocardial function. In animal models, beta-adrenergic stimulation of the heart during cardiopulmonary resuscitation (CPR) has been shown to increase oxygen consumption without improving oxygen supply.[28,29]

Adrenaline seems to increase the time window where it is possible to obtain ROSC.[15] The difference between the short duration of ALS in the 'no adrenaline ROSC' group and the longer duration of ALS in all other groups in the current study reflects this. It is possible that this increased time with low flow, or CPR dependent flow, results in irreparable damage to the brain and other organs in some patients.

The objective of this study was to explore the general development of heart rate and QRS-width during ALS in patients with PEA and the impact of adrenaline on these developments. But such overall trends cannot immediately be applied in decision making when providing care to individual patients. Caveat in mind, the clinical application of these findings may be to pay more attention to the development of heart rate and QRS width during ALS. Narrowing of QRS width and increase in heart rate is a possible marker of an overall positive clinical development that could motivate continuing ALS efforts. It is possible that absence of these changes could be utilized as feedback during ALS, prompting improvements in the ALS efforts or applying concurrent treatment modalities (e.g. fibrinolysis) to improve the myocardial state and thus increasing the probability of ROSC. An increase in QRS width seems to be a negative prognostic sign, even if heart rate increases after adrenaline administration. The time dependent effects of adrenaline could not be assessed in this study; thus, we do not know if QRS width or heart rate increased first in the adrenaline no ROSC group, or if the development of QRS width changed in any way after adrenaline administration. Any such pattern could have clinical impact and the temporal relation between adrenaline administration, heart rate increases and QRS width development is of great interest, and should be studied further.

Limitations

The number of patients included is relatively low and comprised only one pre-hospital emergency response system, potentially limiting generalizability. Whether or not a given patient present with PEA or asystole may depend on several circumstances and patients with initial asystole was not included in this analysis. Unfortunately, the exact time during ALS when adrenaline was administered is not known, as records could not be kept with enough detail in the EMS system. Thus, the immediate time dependent effects of adrenaline could not be examined. Demonstration of a time dependence between adrenaline administration and ECG changes would make the argument that the differences between the adrenaline and no adrenaline groups were due to adrenaline alone stronger.

Some uncertainty applies to the measurements of QRS widths, because of the sometimes aberrant morphology observed in the QRS complexes. A consistent approach to the measurement of QRS width as described in the methods section was utilized to reduce this uncertainty.

Conclusion

In patients with OHCA and initial PEA who obtained ROSC, heart rates increased and QRS widths decreased during ALS. In patients who did not have ROSC, heart rate decreased and QRS width increased, except in patients who did get adrenaline. In this group QRS width also increased, but heart rate increased.

Absence of decrease in QRS width during ALS may be a poor prognostic factor in OHCA with initial PEA.

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Conflict of interest

Gunnar Waage Skjeflo, Jan Pål Loennechen, Eirik Skogvoll, Theresea Mariero Olasveengen and Trond Nordseth declare no conflict of interest.

Lars Wik: NAKOS rep in MAB PhysioControl, Prinicpal investigator for CIRC, LUCAS2 AD study. Patent holder of patents licensed to ZOLL and PhysioControl.

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